REMARKS

Claims 1 - 161 were pending in the application. Claims 1 – 3, 156, 157, 159, 162,166 and 186 have been amended. Claims 4-6 and 35 have been cancelled. No new claims have been added. No new matter has been added by virtue of the amendments and claims, support being found throughout the specification and claims as originally filed.

Support for the amendment to the claims can be found in the specification, in particular at page 19, line 20 – 21 and page 20, beginning at line 23.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Withdrawn Objections/ Rejections

The Examiner has withdrawn the objections to claims 40, 57, 69, 75, 193, 123, 133, 145 and 152.

The examiner has withdrawn the rejection to claims 1, 8, 15 – 18, 24 – 25, 27, 38 – 39, 43 – 51, 54 – 57, 60, 61, 67 – 73, 78 – 8085, 87 – 93, 100 – 102, 105, 107 – 117, 120, 121, 124, 126, 131, 134 and 161 under 35 U.S.C. 102(b) as being anticipated by Klein et al. (US Patent 5,413,686).

Claim Objections

The Examiner has objected to claim 166 because of a minor informality. (Office Action, p.3). Applicants have corrected the spelling error and respectfully request that the objection be withdrawn.

Rejection of Claims Under 35 U.S.C. 103(a)

The Examiner has rejected claims 1- 3, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97 – 98, 100 – 122, 124 – 134, 137 – 139, 142 – 149, 151, 153 – 155, and 159 – 161 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (US Patent 5,413,686; the '686 reference herein), and further in view of Agilent (Agilent capillary electrophoresis system, brochure). (Office Action, p.4).

The Examiner has rejected claims 14, 19 – 23, 99 and 156 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (the '686 reference as above) in view of the Agilent brochure, as applied to claims 1- 3, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97 – 98, 100 – 122, 124 – 134, 137 – 139, 142 – 149, 151, 153 – 155, and 159 – 161 above, and further in view of Colton et al. (Electrophoresis, 1998, vol. 19, pages 367 – 382). (Office Action, p.16).

The Examiner has rejected claims 34, 40 – 42, 150 and 152 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (the '686 reference as above) in view of the Agilent brochure, as applied to claims 1- 3, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97 – 98, 100 – 122, 124 – 134, 137 – 139, 142 – 149, 151, 153 – 155, and 159 – 161 above, and further in view of Katayama et al. (Analytical Chemistry, 1998, vol. 70, pages 2254 - 2260). (Office Action, p.18).

The Examiner has rejected claims 95 – 96, 123, 135, 136, 140, 141, 157 and 158 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (the '686 reference as above) in view of the Agilent brochure, as applied to claims 1- 3, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97 – 98, 100 – 122, 124 – 134, 137 – 139, 142 – 149, 151, 153 – 155, and 159 – 161 above, and further in view of Jardemark et al. (Analytical Chemistry, 1997, vol. 69, pages 3427 - 3434). (Office Action, p.21).

The Examiner has rejected claim 125 under 35 U.S.C. 103(a) as being unpatentable over Klein et al. (the '686 reference as above) in view of the Agilent brochure, as applied to claims 1- 3, 8 – 13, 15 – 18, 24 – 33, 36 – 39, 43 – 94, 97 – 98, 100 – 122, 124 – 134, 137 – 139, 142 – 149, 151, 153 – 155, and 159 – 161 above, and further in view of Couderc et al. (Electrophoresis, 1998, vol. 19, pages 2777 - 2790). (Office Action, p.28).

For the sake of brevity, the rejections under 103(a) are addressed together because each rejection relies on the '686 reference in view of the Agilent brochure in combination with another reference.

Applicants respectfully traverse the forgoing rejections.

The present claims recite a computer program product comprising a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer, wherein the program product comprises instructions for controlling one or more functions of a microfluidic substrate in response to received data regarding one or more substrate properties, wherein the one or more functions comprises scanning a cell based biosensor in electrical communication with an electrode relative to multiple substantially separate fluid streams from one or more outlets of one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels.

No combination of references as cited by the Examiner teaches or suggests the claimed invention.

Nowhere does the '686 reference teach or suggest a computer program product as claimed, where the one or more functions comprises **scanning a cell based biosensor in electrical communication with an electrode relative to multiple substantially separate fluid streams from one or more outlets** of one or more microchannels in the substrate.

Further, none of the Agilent, Colton, Katayama, Jaredemark or Couderc references cure the flaws of the '686 reference. None of Agilent, Colton, Katayama, Jaredemark or Couderc alone or in combination with the' 686 reference teaches or suggests all the elements of the present claims.

The present invention provides an automated workstation for controlling various processes in a microfluidic substrate and for controlling the movement of one or more sensors relative to such a substrate.

Figure 12 illustrates embodiments of the invention as claimed. Figure 12 is shown below:

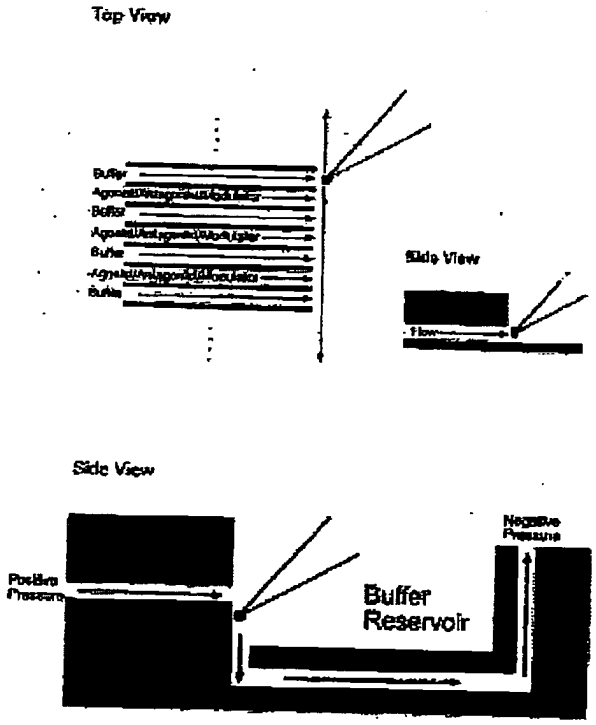

FIGURE 12A-C

Figure 12A schematically depicts an embodiment in which the top view of a microfluidic substrate comprises interdigitating channels and in which a patch-clamped cell is being moved past the outlets of the channels. FIGS. 12B and 12C depict side views of alternate embodiments of the outlets and microchannels. FIGS. 12B and 12C are side views showing a 2D and 3D microfluidic chip design, respectively.

In the description of Figures 11, 12, 13, 14, 15 and 16 on pages 10 – 12 of the specification, Applicants teach that the cell based biosensor may be exposed to a plurality of fluid steams. For example, FIGS. 15A-C show a method for dose-response screening using a microfluidic chip comprising 56 outlets feeding into a sensor chamber, where the screen is performed linearly from channel outlet position 1 to 56. (page 12). As taught in the specification, the patched clamped cells are exposed to substantially separate fluid streams from one or more outlets:

> In one aspect, to achieve dose-response information for agonists, patch-clamped cell(s) in the sensor chamber are moved from the outlet of one microchannel to the next in rapid succession. Microchannels delivering agonists at different concentration are interdigitated with microchannels delivering buffer free of agonist...FIG. 15A is an example of such a loading scheme in a 56-microchannel substrate. Agonist is present at highest concentration in microchannel 52 and then is serially diluted at each subsequent microchannel until microchannel 6....FIG. 15B show simulated patch clamp recordings of agonists at different concentration as described above. From the score sheet for this simulated experiment, i.e., the patch clamp response obtained for each microchannel as shown in FIG. 15C, a dose-response curve can be constructed.

The specification sets forth the meaning of "substantially separate fluid streams" to be "collimated streams with laminar flow." (p.19, line 20). The specification sets forth the meaning of "scanning of a sensor relative to one or more channels in a microfluidic substrate" at page 20, to refer to:

> exposure of the sensor to a plurality of fluid streams from at least one channel in the substrate. This may be achieved by

> moving a sensor past one or more channel outlets in a stationary substrate providing such streams or by moving the substrate relative to a stationary sensor so that it is exposed to streams from one or more channel outlets of the substrate. Scanning may also be achieved by moving both the substrate and the sensor. Exposure to a plurality of fluid streams from a single channel may be achieved by providing different fluid streams (e.g., comprising different agents, or different doses of the same agent, or alternating buffer flow and flow of fluid stream containing an agent, or some combination thereof) from the single channel and/or by intermittently stopping the flow of fluid from an outlet of the channel in proximity to the sensor. In an embodiment where the sensor is stationary, scanning can be done by varying pressure at one or more channels.

The '686 reference is directed to a capillary electrophoresis analyzer that can simultaneously analyze a plurality of samples. (see, column 3). The '686 reference teaches that the first ends of the capillaries are adapted to be collectively transported to and from selected reagent reservoirs (and) (t)he second ends of the capillaries are removably and sealable retained within a common manifold that is in turn in selectable fluid communication with selected reagents and a vacuum source. (see abstract). The Examiner points to Figure 8 and col. 10, lines 22 - 45 of the '686 reference, that teaches that "the analyzer 40 further includes a computer-based control system 590 to control the automated features of the analyzer 40 and to provide a suitable user interface." Applicants direct the Examiner to col. 11, line 23 – col. 14, line 36, where an analysis cycle of the analyzer is described:

> Turntable 100 is rotated to position the first sample tube 132a under the hole 222 and beneath the arc described by the fluid probe 534. The probe 534, in an initial raised park position, is rotated to a position above the first sample tube 132a. ...The pipettor-dilutor assembly 52 is controlled to dispense the sample into the reservoir 144a and also dispense an additional volume of diluent into the reservoir 144a.
>
> The probe 534 is raised, rotated and lowered into the inner fountain 348 of the wash station 346...

The turntable 100 is rotated to position reservoirs 144b and 144c within the reservoir group 142a beneath the wash and buffer reagent tubes 224 and 226, respectively. Valves 520 and 522 are opened for a predetermined time period to dispense running buffer and wash solution into the reservoirs 144b and 144c, respectively.

The above sample, running buffer and wash solution dispensing procedures are repeated for the remaining samples in the sample tubes 132b-132f to dispense diluted sample, running buffer and wash solution into respective reservoirs 144a, 144b, and 144c, respectively, in the reservoir groups 142b through 142f.

(t)he turntable 100 is rotated so as to position the sample ends of the capillaries 200 above the reservoirs 144b in the reservoir groups 142a through 142f that contain running buffer. The elevator stepper motor 154 is controlled to lower the sample end plate 202 until it rests atop the pins 115 and the sample ends of the capillaries 200a through 200f as well as the corresponding electrodes 240 are lowered into the running buffer reservoirs 144b...After a suitable predetermined time period, the vacuum pump 510 and valve 516 are deactivated. The buffer valve 501, auxiliary vent valve 502, and manifold vent valve 507 are opened and the drain valve 508 is closed to complete the filling of the manifold 322 with running buffer by gravity feed from the running buffer bottle 66...

With the manifold 322 filled, buffer valve 501 and auxiliary vent valve 502 are closed...

In order to load sample into the capillaries 200, the elevator stepper motor 254 is controlled to raise the sample end plate 202 such that the ends of the capillaries 200 and the electrodes 240 clear the reagent segments 140. The turntable 100 is rotated to position the sample ends of the capillaries 200 above the sample reservoirs 144a within the respective reservoir groups...The vacuum pump 510 and valves 512, 507 and 508 are operated to apply regulated vacuum to the manifold 322.

> The vacuum pump 510 and valves 512, 507 and 508 are then de-energized to release the regulated vacuum, and the sample end plate 202 is raised, turntable 100 is rotated and sample end plate 202 is again lowered to position the sample ends of the capillaries 200a-200f and the corresponding electrodes 240 into the running buffer reservoirs 144b...
>
> The high voltage power supply 248 is commanded to apply a high voltage across the capillaries 200...
>
> With the electrophoresising voltage applied across the capillaries 200, electrophoretic separation occurs and during the electrophoresising period of, for example, two minutes to four minutes, separated samples (depending upon the mobility of the molecules in the samples) flow past the windows 432 within each of the capillaries 200...The values may are stored as files on one of the disk drives 604 for further manipulation and data analysis and reduction by the control system 590 or external "host" computing means.

The '686 reference nowhere teaches or suggests "substantially separate fluid streams" or "scanning of a sensor relative to one or more channels in a microfluidic substrate" as taught in the present invention.

Clearly, the '686 reference teaches a method that nowhere involves scanning a cell based biosensor in electrical communication with an electrode relative to multiple substantially separate fluid streams from one or more outlets of one or more microchannels in a substrate.

Neither the '686 reference, nor any of the other cited documents disclose or suggest scanning a cell based biosensor relative to multiple fluid steams from one or more microchannels in a substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels as Applicants disclose and claim.

The Examiner argues that the Agilent reference "is a brochure describing the benefits of using an Agilent capillary electrophoresis system for measuring

biolmolecules (and) the fourth page of the brochure measures the migration time of an oligonucleotide sensor." (Office Action, p.5). The Examiner argues that "(t)he brochure itself gives instructions for detecting sensors using the CE apparatus in the form of specification on the penultimate page of the brochure." (Office Action, p.5). Referring to the Figure on the fourth page of the Agilent brochure, the Examiner argues that "(i)t would have been obvious to someone of ordinary skill in the art...to modify the capillary electrophoresis apparatus of (the '686 reference) by use of the sensors, agents and capillary electrophoresis apparatus of the Agilent brochure wherein the motivation would have been that the use of a sensor gives the apparatus an entity which to measure migration time (i.e. the Figure on the fourth page of Agilent)." (Office Action, p.15). The Examiner argues further that "the multiple capillaries in the apparatus with the computer system (of the '686 reference) enable multiple experiments to be performed at once." (Office Action, p.15). The Examiner argues that "while Agilent teaches use of biosensors, the ('686 reference) teaches a multi-channel automated capillary electrophoresis analyzer wherein the samples are analyzed in sequence as they move through the channels (i.e. capillaries)...consequently the combination...teaches the limitations of the instantly rejected claims." (Office Action, p.16).

Agilent fails to remedy the deficiencies of the '686 reference. Agilent merely teaches a CE system that may be used for the analysis of oligonucleotides and other small molecules. The Agilent reference teaches that CE is used to separate ionic species by their charge and frictional forces (see page 8 of brochure). The Agilent reference teaches a method of CE with high resolving power that can be used to separate complex mixtures or closely related compounds (see e.g. page 8 of brochure).

In contrast, the present invention teaches a computer program product, where the one or more functions comprises scanning a cell based biosensor in electrical communication with an electrode relative to multiple substantially separate fluid streams from one or more outlets of one or more microchannels in the substrate. Embodiments of the presently claimed invention are directed to program products, systems, workstations and methods which transport cell based biosensors and the agents which interact with the cell based biosensor via a pressure driven fluid flow. Nowhere does the Agilent brochure disclose or suggest the claimed invention comprising scanning a

cell based biosensor in electrical communication with an electrode relative to multiple substantially separate fluid streams from one or more outlets of one or more microchannels in the substrate.

None of Colton, Katayama, Jaredemark or Couderc remedies the flaws of the '686 and the Agilent references. None of Colton, Katayama, Jaredemark or Couderc teaches or suggests scanning a cell based biosensor in electrical communication with an electrode relative to multiple substantially separate fluid streams from one or more outlets of one or more microchannels in the substrate.

None of the cited references, taken alone or in combination, teach or suggest the present invention as claimed.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejections.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

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Respectfully submitted,

By

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